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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,421	06/13/2005	Evy Lundgren-Akerlund	10142.0003	5691

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,421	LUNDGREN-AKERLUND, EVY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17 and 19-24* is/are pending in the application.

4a) Of the above claim(s) *1-8,13-16,19,20,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-11,17,21 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/6/07, is acknowledged.

2. Claims 1-11, 13-17, 19-24 are pending.

3. Claims 1-8, 13-16, 19-20 and 22-23 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 9-11, 17, 21 and 24 are under consideration in the instant application as they read on a method for detecting atherosclerotic plaque comprising determine the amount of integrin alphal0 chain.

5. Applicant's IDS, filed 12/13/06, is acknowledged, however, reference WO 99/51639 was crossed out because the reference is duplicate of the reference N cited on the PTO-892, mailed on 12/6/06.

6. The following new grounds of rejection is necessitated by the amendment filed on 6/6/07.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 9-11, 17, 21 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The method of claims 9 and 17 are indefinite because the claims are missing the resolution step. It is not clear whether an *increase or decrease* in the amount of integrin alpha10 chain in said mammal relative to control would detect atherosclerotic plaque or determine whether the mammal has or is at risk of developing atherosclerosis.

B. The recitation "the determining" in claims 10-11 lacks sufficient antecedent basis in base claim 9, base claim 9 only recites detecting.

C. The recitation "performed *in vitro*" in claim 11 is ambiguous. It is unclear how the detection of the amount of integrin alpha10 chain in "said mammal" would be done *in vitro*.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 9-11, 17, 21 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/51639.

The `639 publication teaches that the isolated integrin subunit alpha10 can be used as a marker or target molecule for cells during pathological conditions such as atherosclerosis (see page 9, lines 11-37 and Figure 12 in particular). The `639 publication teaches a process of using an integrin alpha 10 subunit as a marker or target molecule of cells or tissue expressing said integrin subunit alpha10, which cell or tissues are of animal including human origin (see published claim 28), which process is used during pathological conditions involving said subunit alpha10 (see published claim 25). Further, the `639 publication teaches using binding entities having the capability of binding specifically to an integrin subunit alpha10 as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin (see page 7, lines 30-33 in particular). Also, the `639 publication teaches polyclonal antibodies as a binding entity in immunohistochemical staining of α10 in different tissues (see Example 6) and a secondary antibody conjugated to peroxidase (see Example 11 on pg. 25 in particular). Fig. 13(c) depicts immunostaining of heart valves in 3 day mouse limb.

Regarding the control, since the `639 publication teaches that alpha10 as a marker for atherosclerosis, then the expression of alpha10 must compared/scored against a control. Actually, fig. 12 provides several negative controls (-) compared to aorta (+++) score.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 6/6/07, have been fully considered, but have not been found convincing.

Applicant submits that the reference does not relate to the use of any binding agent for the detection of atherosclerotic plaques or the diagnosis of atherosclerosis (emphasis added by Applicant). The `639 does not disclose if and how expression of integrin alpha10 is altered in atherosclerosis, and the `639 simply makes no mention of atherosclerotic plaques or the utility of integrin alpha10 for diagnostic purposes. Applicant contends that there is no disclosure that integrin alpha10 could be used as a marker for detection of atherosclerotic plaque or the diagnosis of atherosclerosis. Applicant concludes that the `639 publication can not anticipate this claim.

The Examiner points to Applicant's Remarks, filed 6/6/07, on page 10 top ¶ for further support that that the aortic tissue used for the assessment of integrin alpha10 mRNA expression in the

aorta in Figure 12 of the `639 publication is likely to have contained atherosclerotic plaque. A prior art reference must be considered in its entirety, see MPEP 2141.02. Given that the immunohistochemistry was able to detect alpha10 protein expression in cryo-sections form heart valve, and that atherosclerotic plaque is a pathological condition of the heart, the antibody would detect the atherosclerotic plaque. Contrary to applicant assertion, the `639 publication teaches the a process of utilizing a binding entities (e.g. antibodies) having capability to binding alpha10 as amarkers or target molecules of tissues expressing said integrin subunit alpha10 (see page 7, lines 24-33 in particular).

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 9-11, 17 and 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/51639 in view of US. Pat. No. 6,458,590.

The `639 publication teaches that the isolated integrin subunit alpha10 can be used as a marker or target molecule for cells during pathological conditions such as atherosclerosis (see page 9, lines 11-37 and Figure 12 in particular). The `639 publication teaches a process of using an integrin alpha 10 subunit as a marker or target molecule of cells or tissue expressing said integrin subunit alpha10, which cell or tissues are of animal including human origin (see published claim 28), which process is used during pathological conditions involving said subunit alpha10 (see published claim 25). Further, the `639 publication teaches using binding entities having the capability of binding specifically to an integrin subunit alpha10 as a marker or target molecule of cells or tissues expressing said integrin subunit $\alpha 10$, which cells or tissues are of animal including human origin (see page 7, lines 30-33 in particular). Also, the `639 publication teaches polyclonal antibodies as a binding entity in immunohistochemical staining of $\alpha 10$ in different tissues (see Example 6) and a secondary antibody conjugated to peroxidase (see Example 11 on pg. 25 in particular). Fig. 13(c) depicts immunostaining of heart valves in 3 day mouse limb.

The claimed invention differs from the reference teachings only by the recitation of a control.

The `590 patent teaches that the data unambiguously demonstrate (a) expression of $\alpha v \beta 3$ integrin protein in CASMCs in the arteries of control and atherosclerotic patients [as detected by immunofluorescence], (b) remarkable elevation in the expression of OPN-mRNA [as detected by in situ hybridization and RT-PCR] and OPN protein [as detected by visual inspection and densitometric analysis of Western blots] in CASMCs in the arteries of patients suffering from coronary atherosclerosis as compared to healthy individuals, (c) remarkable sustained elevation of OPN protein levels in the serum of arterial atherosclerotic patients following DCA procedure

as compared to the levels in healthy controls and to atherosclerotic patients who did not undergo DCA (see col. 24, lines 47-60 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform a control as taught by `590 patent in the method of detecting atherosclerotic plaque taught by the `639 publication. Further, the `639 publication taught performing control implicitly because in order for a10 to be a marker for atherosclerosis, α10 must be compared to a control.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because to compared to the levels in healthy controls and to atherosclerotic patients as taught by the `590 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 6/6/07, have been fully considered, but have not been found convincing.

Applicant submits that page 9 of WO 99/51639 only relates to the use of polynucleotides or oligonucleotides for determining the differentiation-state of certain cells. It does not contemplate the use of antibodies that can bind integrin alphal0 protein expressed on the cell surface. However, claim 9 has now been amended to be limited only to anti-integrin alphal0 antibodies as binding agents.

However, a prior art reference must be considered in its entirety, MPEP 2141.02. The `639 publication further teaches a process of using an integrin alpha 10 subunit as a marker or target molecule of cells or tissue expressing said integrin subunit alphal0, which cell or tissues are of animal including human origin (see published claim 28), which process is used during pathological conditions involving said subunit alphal0 (see published claim 25). Further, the `639 publication teaches using binding entities having the capability of binding specifically to an integrin subunit alphal0 as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin (see page 7, lines 30-33 in particular). Also, the `639 publication teaches polyclonal antibodies as a binding entity in immunohistochemical staining of α10 in different tissues (see Example 6) and a secondary antibody conjugated to peroxidase (see Example 11 on pg. 25 in particular). Fig. 13(c) depicts immunostaining of heart valves in 3 day mouse limb.

Applicant submits that W099/51639 does not disclose the use of any binding agent for the detection of atherosclerotic plaques or the diagnosis of atherosclerosis. W099/51639 does not disclose if and how expression of integrin alphal0 is altered in atherosclerosis, and W099/51639

simply makes no mention of atherosclerotic plaques or the utility of integrin alpha10 for diagnostic purposes. There is also no disclosure that integrin alpha10 could be used as a marker for detection of atherosclerotic plaque or the diagnosis of atherosclerosis.

Contrary to Applicant submission, the `639 publication teaches that the isolated integrin subunit alpha10 can be used as a marker or target molecule for cells during pathological conditions such as atherosclerosis (see page 9, lines 11-37 and Figure 12 in particular). Further, the Examiner points to Applicant's Remarks, filed 6/6/07, on page 10 top ¶ for further support that that the aortic tissue used for the assessment of integrin alpha10 mRNA expression in the aorta in Figure 12 of the `639 publication is likely to have contained atherosclerotic plaque. Given that the immunohistochemistry was able to detect alpha10 protein expression in cryo-sections form heart valve, and that atherosclerotic plaque is a pathological condition of the heart, the antibody would detect the atherosclerotic plaque. Contrary to applicant assertion, the `639 publication teaches the a process of utilizing a binding entities (e.g. antibodies) having capability to binding alpha10 as amarkers or target molecules of tissues expressing said integrin subunit alpha10 (see page 7, lines 24-33 in particular).

Applicant submits that page 7 of WO99/51639 cited by the Examiner relates to the use of binding entities against integrin alpha10 as markers of cells expressing integrin alpha10. The examples 6 and 11 of WO99/51639 cited by the Examiner relate to the preparation of an anti-integrin alpha10 antibody and to the use of such an antibody for the immunohistochemical staining of integrin alpha10 in fascia around tendon and skeletal muscle and in tendon structures in heart valves. However, these examples do not disclose the use of anti-integrin alpha10 antibodies for the detection of integrin alpha10 in either normal artery tissue or atherosclerotic plaques.

A prior art reference must be considered in its entirety, MPEP 2141.02. Contrary to Applicant assertions the `639 publication teaches that the isolated integrin subunit alpha10 can be used as a marker or target molecule for cells during pathological conditions such as atherosclerosis (see page 9, lines 11-37 and Figure 12 in particular). The `639 publication teaches a process of using an integrin alpha 10 subunit as a marker or target molecule of cells or tissue expressing said integrin subunit alpha10, which cell or tissues are of animal including human origin (see published claim 28), which process is used during pathological conditions involving said subunit alpha10 (see published claim 25). Further, the `639 publication teaches using binding entities having the capability of binding specifically to an integrin subunit alpha10 as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin (see page 7, lines 30-33 in particular). Also, the `639 publication teaches polyclonal antibodies as a binding entity in immunohistochemical staining of α10 in different tissues (see Example 6) and a secondary antibody conjugated to peroxidase (see Example 11 on pg. 25 in particular). Fig. 13(c) depicts immunostaining of heart valves in 3 day mouse limb.

Further, Applicant submits that the teachings of the '590 patent cited by the Examiner relate to a comparison of OPN expression in coronary artery tissue from patients with severe atherosclerosis in coronary arteries who underwent directional coronary atherectomy (DCA) and from individuals with no evidence of atherosclerosis who did not undergo DCA. Thus, the tissues of two very distinct, distinguishable groups of individuals are compared: one group that underwent DCA, and another group that did not. Hence, in this experimental setup there is a defined group of individuals, i.e. those who did not undergo DCA, who can serve as a control for those individuals who underwent DCA. This is very different from the experimental setup in the instant invention and is also not suitable for individual diagnosis. Here, the disclosed methods are aimed at detecting atherosclerotic plaque in individuals who did not undergo DCA. The purpose is to detect the development of atherosclerotic plaque which occurs in all individuals to varying degrees. Hence, the control group used in the '590 patent would not be a suitable control group for the methods of the instant invention. Rather, in the instant methods the control is the normal artery tissue that is spatially separate from atherosclerotic plaque but within the same individual in whom the atherosclerotic plaques are to be detected. As discussed above, integrin alpha10 protein expression is detected in the atherosclerotic plaque but not in the normal artery tissue.

However, a person of ordinary skill has good reason to pursue a relative control within his or her technical grasp. The resultant control is likely the product not of innovation but of ordinary skill and common sense. Further, since the `639 publication teaches that alpha10 as a marker for atherosclerosis, then the expression of alpha10 must compared/scored against a control. Regarding the issue that the control in the instant method is normal tissue that is spatially separate from atherosclerotic plaque but within the same individual in whom the atherosclerotic plaques are to be detected. It is noted that Applicant is arguing limitations that are not claimed.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 11, 2007

Maher Haddad

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